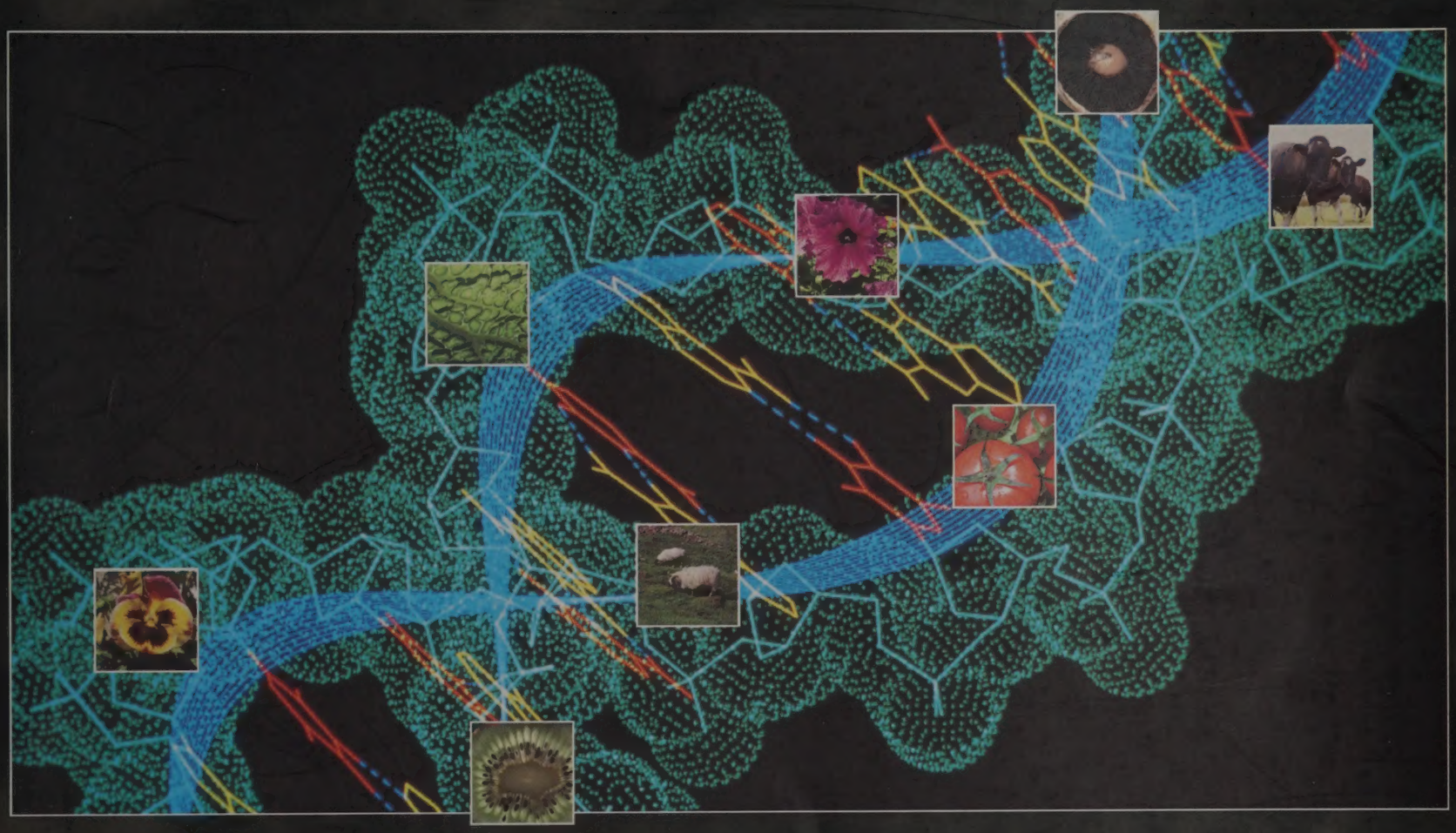
GENETIC MODIFICATION



RISKS AND SAFEGUARDS

HSC
Health & Safety Commission

A REPORT BY THE ADVISORY COMMITTEE ON GENETIC MODIFICATION

First published 1995

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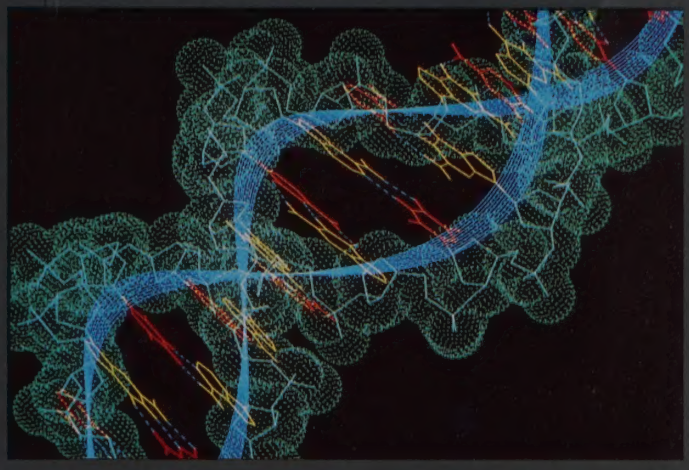

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GENETIC MODIFICATION

HSE BOOKS

FOREWORD

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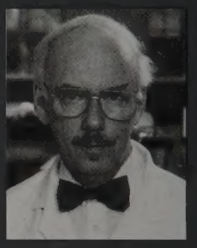
The exciting techniques of genetic modification are still new. Many of its applications can be foreseen only dimly as yet. But it is certain that gene technology will transform the world in which we live. Its applications have already led to major improvements in the procedures and products of agriculture, medicine and industry, and will continue to affect profoundly these and many other areas of human activity. Gene technology is also down to earth: the science fiction writer's flights of fancy are entertaining but have little to do with reality. As with other types of science and technology, we have to make sure that both the procedures and the applications of genetic modification are safe and that we do not harm either human beings or the environment.

That is what this booklet is about. The story is told from the standpoint of one of its participants, the Health and Safety Commission's Advisory Committee on Genetic Modification (ACGM). ACGM has had a major influence in the development of safety principles for biotechnology, and we unashamedly celebrate that here. At the same time, our aim is to be informative: not to present genetic modification either as a bogy or as a panacea, but to make possible a clear-sighted view of a valuable technology that can be managed safely.



Sir Hans Kornberg, ScD, FRS

As the chairman of ACGM for most of the last decade, and as someone who has spent many years in the study of life processes at the molecular level, I have been privileged to see the events described here unfold. These events form an important chapter in the history of harnessing biological knowledge to useful ends. I believe that this story of astonishingly rapid yet safe progress is a story well worth telling, and I hope that you too will find it so.

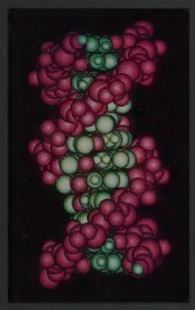
Sir Hans Kornberg, ScD, FRS

Chairman of ACGM

INTRODUCTION

Since it began in the early 1970s, the science and technology of genetic modification has made startling progress. Such is its potential to change our lives with new products and new techniques - in medicine, food production, industry - that it is sometimes referred to as the next industrial revolution. Its economic potential is huge.

It has also been one of the safest technologies ever developed and, judging by its record, seems to need little in the way of regulatory control. But it is a technology that does produce novel organisms, and they may affect people and interact with the environment in new and possibly harmful ways. For that reason it has been and still is considered wise to have in place procedures and regulations that will safeguard against the possibility of mishap. What is needed is a framework of controls that provides the right level of protection while allowing society to reap the benefits.



Computer generated graphic of a segment of the DNA molecule

Such a framework has to keep pace with developments in the science and technology of genetic modification. Regulators need expert advice to enable them to make sure that it does. Much of the advice on which the UK government has based its strategy for regulation has been provided by the Health and Safety Commission's Advisory Committee on Genetic Modification. This booklet acknowledges the tenth anniversary of the setting up of the committee in its present form, and outlines what it does and has achieved.

The idea of genetic modification (or 'genetic engineering' as it is sometimes called) is now cropping up in newspapers, films and on television, and many people have heard of it and are intrigued by it. Terms like 'genes' and 'DNA' are entering everyday language. But far fewer know what sort of controls have been put in place to keep this absorbing new technology safe, or the kind of thinking that has gone into them. This booklet aims to fill that gap, to help the reader take part in a more informed way in a continuing debate on a subject of great public interest and importance.

There is a glossary of unfamiliar terms at the back of the book.

CONTENTS

TECHNIQUES OF GENETIC MODIFICATION

Genetic modification uses several standard methods to allow genes to be extracted, modified, and inserted into a cell. Scientists have mimicked natural processes, using the enzymes which copy, repair and decode DNA in the normal cell to modify it in the test tube.

An important requirement is a means of putting the modified DNA into a cell so that it is inherited by all the offspring of that cell. This is usually done by what is called a 'vector'. Types of vectors and the most effective ways of getting them into cells vary between different organisms. The type of vector used is often an important consideration in assessing the safety of the modified organism.

BACTERIA: the normal vectors for bacteria are derived from DNA molecules called 'plasmids', which can replicate independently and which occur naturally in many cells, or from viruses called 'phages' which infect bacteria.

BIOTECHNOLOGY Genetic modification is part of the general field of biotechnology. Broadly speaking, biotechnology is the use of living organisms to make or do things of value to human beings or the environment. In this sense, biotechnology is very old. From the earliest days of animal and plant breeding, brewing and breadmaking, human beings have made use of biotechnological processes.

What might roughly be called 'modern biotechnology' dates back to the 1940s and 50s. Modern techniques in biochemistry and engineering made it possible to modify and grow organisms, especially microbes, in sophisticated ways to produce complex and valuable substances. Antibiotics and enzymes are notable examples.

Later, the capabilities of biotechnology were enormously increased by advances in molecular biology and genetics. It became possible to make planned alterations to organisms at the molecular level, to achieve even more finely controlled results.

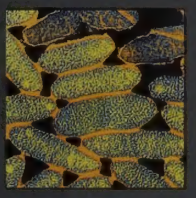
This powerful set of techniques is genetic modification.

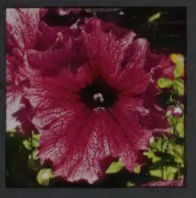
GENETIC MODIFICATION Living things take their form and function from the information coded in their genes. Copies of an organism's genes are carried in each one of its cells. It is the passing on of genes from generation to generation, with the information contained within them, that ensures that an acorn grows into an oak and not an ash, and that the combination of human sperm and egg cells grows into a new human being resembling its parents and ancestors.

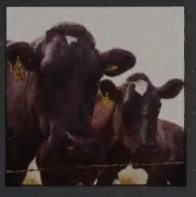
Genes are made from a chemical called DNA. DNA molecules are long chains made up from a few basic components repeated in varying patterns. It is the patterning of those repeated components, different in each individual, that carries the coded genetic information. Genetic modification is the ability to alter the DNA so as to change the

C M O D I F I C A T I O N ?

Flowers can be genetically engineered to produce different colours







A sample tube containing a pellet of human DNA (white)

nature of the organism, to give it new and beneficial characteristics or to remove harmful or undesirable ones.

Genetic modification is possible only up to a point. We can make tomatoes that keep longer, chrysanthemums with a different colour, and bacteria that can break down pollutants, but not mermaids or dinosaurs.

PLANTS: modification of some plant cells makes use of vectors derived from plasmids found in a common plant pathogen called Agrobacterium which can inject DNA into a plant cell.

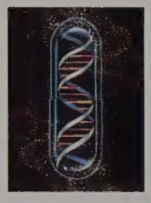
ANIMALS: many important studies on human disease or new pharmaceuticals use animal, including human, cells cultured in the laboratory. Vectors for such cells, and for whole animals and human therapy, are often derived from viruses. Because most viruses are pathogenic, it is important to ensure that they are properly disarmed and are safe.

Most vectors include a method of detecting their presence in the cell. Such markers can include antibiotic resistance genes or enzymes which produce a colour change in the presence of certain chemicals. Marker genes may also raise concerns over safety if they give the modified organisms potentially undesirable characteristics.

CURRENT USES OF GENETIC MODIFICATION

Current uses of genetic modification include:

- **improved vaccines. A vaccine against the hepatitis B virus is now safely produced by genetically modifying a harmless organism (such as a yeast) to produce proteins from the virus which are then purified and made into a vaccine;**
- **pure and safe medicinal products (such as insulin, blood factor VIII and human growth hormone). These were formerly produced from humans or animals and some carried a slight risk of transmitting disease; pure and safe equivalents are now produced using genetically modified organisms;**
-



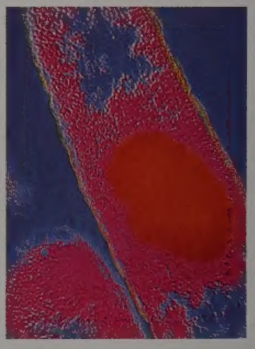
Genetic modification arouses strong feelings in people. Some of the negative ones are because it is thought to be unnatural or immoral, or too dangerous. More positive feelings are sometimes held by people who see genetic modification as a means of satisfying a wide range of human needs in a sustainable way. This booklet does not go into questions of ethics or taste, nor does it try to persuade readers that genetic modification is inherently good or bad. It describes only the steps that have been taken to make sure that when the technology is used it is used safely.

Those steps have always aimed to make it possible for people to have the benefits of genetic modification without being exposed to any risks that may arise from it.

THE BENEFITS Genetic modification makes it possible to tailor organisms to be safer, more specific and more productive in what they do than their unmodified counterparts. They can be given the ability to produce valuable substances that would otherwise be in short supply. Modified organisms can sometimes substitute cleanly and safely for traditional, biological and chemical-based processes that are dangerous or polluting.

THE RISKS Some of the harmful consequences of genetic modification that have been thought possible are that:

- more infectious or drug-resistant micro-organisms might be produced;
- harmful genetic material, for example material associated with cancer, might be transferred via a genetically modified organism (GMO) to a human being;
- a genetically modified plant might be aggressive and colonise its environment, eliminating plants already living there;
- genetic material from a modified plant might be transferred to a related plant that is considered a weed, making it more competitive, for example by giving it herbicide resistance;
- modified micro-organisms might interfere with the natural recycling of nutrients in the environment.



ENETIC MODIFICATION?

- crop plants which are immune to diseases or herbicide tolerant;
- tomatoes which do not produce the enzyme which makes them squashy, allowing them to be picked later and to develop a better flavour;
- bacteria specifically modified to degrade toxic environmental pollutants such as PCBs and dioxins;
- faster and more effective scientific research into major diseases such as cancer and AIDS.

False colour transmission electron micrographs of bacteria genetically engineered to produce vaccines

RISK ASSESSMENT AND THE

PRINCIPLES OF RISK ASSESSMENT

There is a widely accepted structure for carrying out a risk assessment. It is broken down into defined stages as follows:

1 Identify all of the possible harmful events that could be associated with the organism or the work being done.

2 Estimate how likely it is that these events will actually occur, by considering the properties of the organism, the people, plants, animals and environment that could be affected, and the type of work and equipment being used.

3 Determine for each event how serious it would be if it were to occur: would it be trivial or very damaging, or somewhere in between?

4 Decide on the overall level of risk - by combining all the above factors for all the hazards.

5 Finally, adopt appropriate safeguards and check that they will adequately control the risks.

RISK ASSESSMENT Before the right controls can be chosen for a risk it must be assessed. That means coming to a judgement about three things: what *might* happen; how likely it is that it *will* happen; and if it did, how serious that would be.

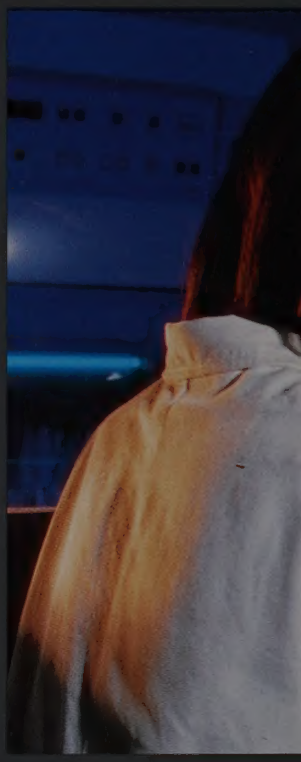
These judgements are becoming easier in genetic modification, but were quite difficult in the beginning. It was hard to be confident that all of the possible harmful effects had been thought of, and for those that had been, their likelihood was often not well understood. And sometimes there is still disagreement about how much a particular alteration of the natural or human-made environment would matter, and even about whether it should count as harmful or beneficial.

In other words, one of the leading features of risk assessment in genetic modification was, and to a degree still is, uncertainty.

DEALING WITH UNCERTAINTY: PRECAUTION OR PREVENTION? Health and safety law, or law aimed at protecting the environment, is often introduced after something has gone wrong, for example because a particular machine has caused accidents or because a chemical has harmed people or wildlife. The law can then be targeted at a known risk and the effects of it can be measured. In other words it is introduced in reaction to events and to prevent harm that we know will otherwise happen.

The law relating to genetic modification has for the most part not been like that. Because of the uncertainty it has faced, it has had to be precautionary; that is, an attempt to make sure that possible and even unforeseen dangers (if any) do not cause actual harm before they can be fully understood. Gradually, as knowledge increases, precautionary safeguards can be replaced by better targeted, preventative ones based on scientific understanding of real possibilities.

Researcher using a microscope to examine a cell culture taken from a patient affected by a genetic disease



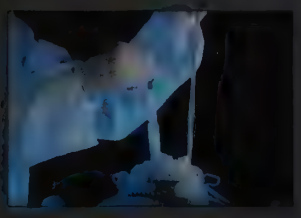
Cryogenic storage of DNA: tissues containing DNA for research are stored in liquid nitrogen at -196 degrees centigrade

DEVELOPMENT OF CONTROLS

THE DEVELOPMENT OF CONTROLS The early fears about genetically modified organisms provoked a strong reaction. Scientists working in the field were themselves alarmed, and 1974 saw the unusual situation of scientists restricting their own research, by voluntarily banning work on certain organisms while the risks were assessed and controls put in place. Governments anxious to make sure that nothing went

wrong began to introduce safeguards in a process that is continuing to this day.

This process over the last twenty years has been one of refining such controls in parallel with the growth of knowledge about the true risks. Greater understanding has meant that while not all of the early fears have entirely gone away they are now seen as ▶



THE UK - A LITTLE HISTORY

In 1974 the government set up a working party under Lord Ashby to consider what should be done in the UK. It gave the new technology the 'amber light', recommending that with strict safeguards it should be allowed to continue because of the potentially great benefits.

Another working party under Professor Robert Williams took things forward in 1976. It drew up a code of practice for laboratory work with GMOs. It recommended the formation of a Genetic Modification Advisory Group (GMAG) to examine proposals for GMO work, and saw this as a way to build up a body of experience and 'case-law'. It proposed that regulations under the Health and Safety at Work etc. Act 1974 (HSW Act) should make notification to GMAG compulsory.

GMAG was set up and in the following years published a number of influential reports (listed in the Further information section) which laid the foundations for current guidance on risk assessment and control. Notification regulations were ▶

Production of genetically engineered pharmaceuticals (reproduced by permission of British Bio-technology Group plc)

▶ introduced in 1978 covering the actual modification of organisms.

In 1984, GMAG became the Health and Safety Commission's Advisory Committee on Genetic Modification (ACGM). In 1989, the regulations were extended to cover also the use of GMOs and the release of GMOs to the environment, though the purpose of the legislation was restricted to the protection of human health. EC directives on GMOs led in 1993 to the two sets of regulations that we have now, dealing separately with contained use and deliberate release, and with the protection of both human health and the natural environment.

As the deliberate release of GMOs into the environment became a real issue in the late 1980s, a new committee split off from ACGM to deal with this area: the Advisory Committee on Releases to the Environment (ACRE). The two committees are now largely independent, with ACGM overseeing genetic modification activities in containment and ACRE the release of GMOs and the marketing of GMO products.

▶ less likely to be realised in a disastrously uncontrolled way, especially as far as human health risks are concerned.

There are two main reasons for this. One is that it is increasingly clear that the combination of events that would be necessary to produce a harmful organism accidentally is very improbable. The other is a growing confidence in the controllability of the technology - the degree to which organisms can be designed to be safe.

This has changed the way in which risk is assessed. For example, in the early days it was thought that the unpredictable effects of transferring genetic material from one species to a very different one, or using an 'impure' mixture of DNA fragments, were the things to be most worried about. Outlandish results were feared. Now we are more interested in assessing the effects of planned and relatively small changes to a familiar organism.

As a result, the regulation and control of genetic modification have become more and more like those of other potentially hazardous activities. They are increasingly concerned with the foreseeable consequences of intentional acts, as the area of the unforeseen and unpredictable grows smaller.

ACGM: WHAT DOES IT DO?

ACGM is one of a number of advisory committees set up by the Health and Safety Commission (HSC) to advise it on a range of industrial sectors and types of activity. Some of ACGM's members represent employers and workers, and others are independent experts in the science and technology of genetic modification (see Appendix for details of ACGM's membership since 1984). ACGM does three things:

- prepares guidance on how to work safely;
- examines proposals from people who want to work with GMOs;
- advises the HSC and the government on policy and law.

ACGM GUIDANCE ACGM guidance has been developed into a compendium of guidance notes, covering principles of risk assessment, the selection of control measures, and special advice on particular kinds of GMO work. They are summarised in the box.

EXAMINATION OF PROPOSALS FOR GENETIC MODIFICATION WORK Looking at proposals for GMO work and advising on whether or not they were likely to be safe was GMAG's original purpose, and has always been an important part of GMAG's and then ACGM's work. This is where the committee acts most directly as a safeguard against mishap. In the early days any proposal to undertake genetic modification was discussed in detail. As knowledge of the risks and guidance on assessment was developed, the need to scrutinise low-risk work was reduced. At present, ACGM examines only proposals for high-risk or particularly novel work and much of this is done by postal circulation or in specialist sub-groups of the committee. As a result of this scrutinising role, GMAG and then ACGM have between them been closely involved in a number of key stages in the development of genetic modification technology.

ACGM GUIDANCE NOTES

Note 1 - *Work with cancer genes*

Note 2 - *Safe host and vectors* (now in Note 7)

Note 3 - *Deliberate release of GMOs* (now withdrawn)

Note 4 - *Health surveillance*

Note 5 - *Risk assessment for viruses*

Note 6 - *Large-scale work*

Note 7 - *Risk assessment for bacteria*

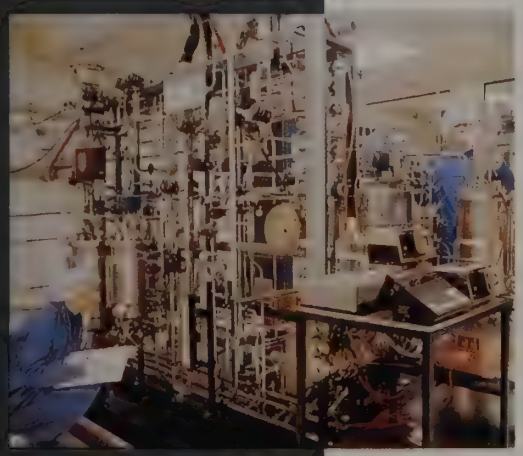
Note 8 - *Laboratory safety*

Note 9 - *Modified animals*

Note 10 - *Modified plants*

Note 11 - *Local safety committees*

The latest compendium of guidance notes can be obtained from the ACGM Secretariat. See the Further information section for details.



DNA electrophoresis: scientist looking at DNA fragments in an electrophoresis cell. The fragments have been stained with ethidium bromide. This fluoresces under UV light and makes viewing easier. A face visor is worn for eye protection from the UV light.

RESEARCH: WHERE IT ALL BEGINS Much of the work carried out so far using genetic modification has been in research and development, either as the first stage in the development of a practical application or with the techniques of modification being used as a tool in fundamental biological research. This field has therefore up to now been the main focus of attention for regulation and control, and early requirements and guidelines were largely aimed at the laboratory.

Even so, most laboratory work is low risk, involving for example the cloning of genes into bacteria so that their coded information can be examined (DNA sequencing). Higher risk work might involve the modification of organisms that are already human pathogens, or the insertion of genetic material that is itself potentially harmful, for example genes that are associated with cancer.

Genetic modification is widely used in academic, medical, agricultural and commercial research and development. Most universities, large hospitals and research institutes together with commercial companies engaged in pharmaceuticals, biotechnology or plant breeding have notified genetic modification work to HSE. In 1993 there were 420 notified premises where 3500 new projects were started at the lowest level of risk. About 75 research projects, mainly on disease prevention, were notified at the higher levels of risk. In total, there are approximately 20 000 projects involving genetic modification research in the UK.

GMAG and ACGM have also naturally spent much of their time developing guidance on risk assessment and containment for research activities, and scrutinising research proposals. As the technology has developed, attention has shifted from work involving bacteria to the modification of viruses, animals and plants.

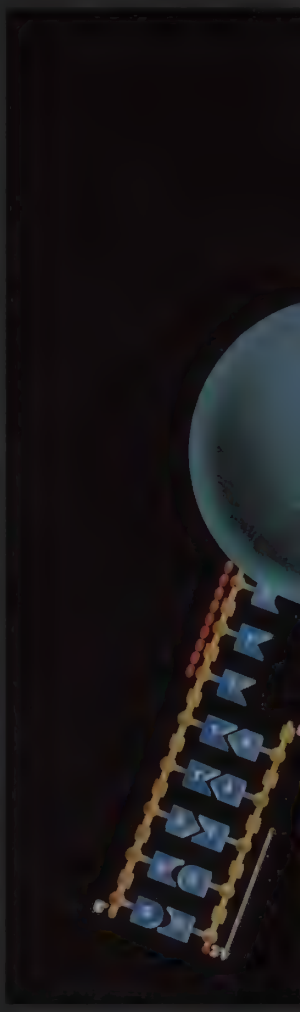
LARGE-SCALE WORK To secure all the benefits of genetic modification, the technology must be exploited in commercial and industrial processes. Some of these will be small-scale (for example some medical applications and production of fine chemicals) and little different from research in the safety problems they create. But often we want as much

ACGM GUIDANCE FOR RESEARCH WORK

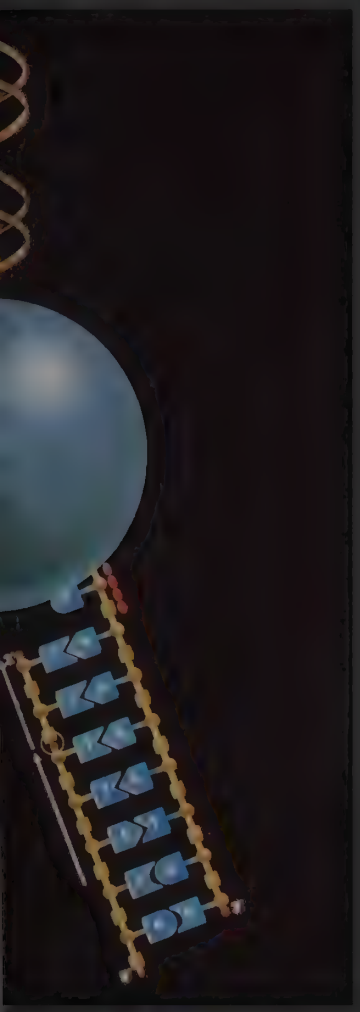
There are three main ACGM guidance documents which give advice on how to assess the risks to human health and the environment and how to control any risks.

ACGM Note 7 covers the risk assessment of work with genetic modification bacteria and the selection of control measures, to protect both the health of researchers within the establishment and the wider environment against escape of the organism. Much of the guidance is aimed at encouraging the use of intrinsically safe (disabled) host bacteria and vectors.

ACGM Note 5 provides similar guidance for work with viruses, including those that are pathogenic for humans or animals.



A mechanism for replication of DNA. The two antiparallel strands of nucleotides are joined through hydrogen bonding between the bases adenine (A), thymine (T), guanine (G) and cytosine (C)



of a product as production engineering can provide, and that means large-scale processes.

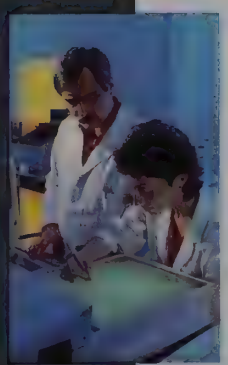
In the early days there were understandable fears about scaling up, simply because it is intrinsically more difficult to contain large quantities of anything. But two other factors have lessened those fears:

- large-scale processes are not embarked upon until they have been tried and tested and understood. The equipment is designed to be reliable and there is strong commercial pressure for it to be operated safely and reliably;
- the great advantage of genetic modification is that the genes having the sought-after effect can be put into organisms tailored for safety (production of the hepatitis vaccine mentioned on page 4 is an example). In fact it will generally be true that controls are needed more to protect the process and product from the outside world than vice versa.

For these reasons, although large-scale work is certainly seen as having its own features and place in the regulatory framework, it is not now regarded as especially hazardous in itself.

Early attention was given by the Organisation for Economic Co-operation and Development (OECD) to the setting down of principles of safe working on a large scale. It drew up a set of influential guidelines in a 1986 publication called *Recombinant DNA safety considerations.* This covered the control measures that should be applied, and also established criteria for identifying genetically modified organisms that could be used without special containment measures, because they were no more dangerous than naturally occurring non-pathogenic organisms. This range of organisms was to be covered by what was described in the OECD guidelines as 'good industrial large-scale practice' (GILSP). Members of ACGM and HSE played an important part in shaping these guidelines and they reflected to a large extent the principles that had been developed by ACGM and GMAG together with UK industry. In turn, the later EC directives on genetic modification were partly based on the OECD guidelines.

ACGM Note 8 details the safety measures required in four, increasingly stringent, levels of laboratory containment (ACGM levels 1 to 4). Level 1 is the most widely used and is for harmless organisms (such as yeast or non-pathogenic bacteria), and the containment measures increase through level 2 (for work with pathogens such as the virus that causes common colds), level 3 (for work with pathogens which cause diseases such as anthrax and AIDS) to the maximum level 4 laboratories (for rare and dangerous diseases such as Lassa fever). There have not been any genetic modification activities requiring level 4 containment in the UK.



Scientists examining DNA sequencing autoradiogram over a light box

Large-scale plants (of between, say, 500 litres and 200 000 litres) are expensive and sophisticated and are therefore not widespread. In 1993, there were about 75 registered premises which were equipped for large-scale work. Only eight new large-scale projects were notified to HSE in 1993.

Despite these small numbers, the UK biotechnology industry (not all of which use genetically modified organisms) includes over 600 companies and academic institutions. The market for biotechology-derived products is worth approximately $500 million and is growing at approximately 20 to 30% per annum.

ACGM GUIDANCE FOR LARGE-SCALE WORK

The main source of guidance for large-scale work is ACGM Note 6 which builds upon the main risk assessment guidance in ACGM Note 7, and outlines the engineering and managerial controls necessary to protect the health of the workforce, others outside the facility and the wider environment (including the provisions for waste treatment). Note 6 currently provides a differentiation between safe organisms for which no specific physical controls are needed and those of higher risk for which a further three levels of containment are specified.

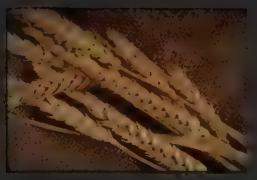
RELEASE INTO THE ENVIRONMENT Industrial processes are generally still 'contained use'. In other words, it is only in the case of an accident that live genetically modified organisms will escape into the environment. Some applications however are possible only if the organism is deliberately released, or placed on the market without it being assumed that the purchaser will keep it in containment.

There are many potential uses of organisms allowed to go free in this way. Crop plants can be made more productive and disease resistant. Micro-organisms can be modified to enable them to prey on pests while being otherwise harmless, or to destroy polluting substances without the need for expensive chemical processing. A growing field of application is in medicine, where, for example, live genetically modified micro-organisms can be used as vaccines.

There are estimated to have been over 2000 deliberate releases world-wide and over 160 in the UK alone. The majority have involved crop plants, but others include bacteria that nodulate plant roots; viruses targeted at insect pests; and animal vaccines against diseases such as rabies.

Several genetic modification products are now on the market. Many of them are intended for specialist uses such as laboratory research and animal vaccines, but crop plants are now moving towards the market in Europe.

There are concerns about the release of modified organisms, however. They centre



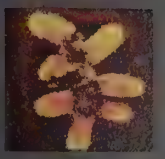
not so much on the chance that a super-bug or Frankenstein's monster may be produced, as on the possibility that the modified organism may disturb the environment in more subtle ways. A modified plant, for example, might be unexpectedly good at taking over from native ones, or might transfer new genetic material to an unintended host and make it more competitive. Of course this sort of disruption can happen without genetic modification being involved at all; probably no-one foresaw when rabbits were taken to Australia that they would be such successful colonisers.

The complexity of the environment, and the life-forms that live in it, means that these effects are sometimes hard to predict. The controls and safeguards applied to deliberate release are therefore based on strict scrutiny of proposals and on a cautious step-by-step approach. Limited and monitored trials are carried out before more general release is permitted.

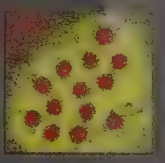
ACGM AND ACRE Aware of these concerns, ACGM produced initial guidelines in 1985 on safe procedures for deliberate release, and formed a specific sub-group, the Planned Release Sub-Committee (PRSC), to keep them up to date and oversee this branch of the technology. The PRSC was an important source of advice to the Royal Commission on Environmental Pollution (RCEP), and to the Department of the Environment (DoE) when, acting on the RCEP's recommendation, it prepared the sections of the 1990 Environmental Protection Act that deal with genetically modified organisms.

DoE meanwhile had formed a committee (the Interim Advisory Committee on Introductions (IACI)) which advised on the introduction of new species, including non-indigenous species imported into the country. In 1990 the Advisory Committee on Releases to the Environment (ACRE) was formed, replacing both the PRSC and the IACI, operating more or less independently of ACGM in advising on all aspects of the increasingly wide range of releases taking place. In 1993 it was placed on a statutory footing, and now has the function of advising the Secretary of State under section 124 of the Environmental Protection Act. ACGM and ACRE work closely together, and have some members in common.

VIRUSES

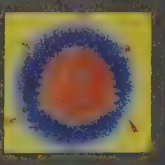


Rabbit viruses



Hepatitis A viruses

AIDS viruses



Common cold viruses

THE INTERNATIO

The potential of genetic modification technology for changing the world, and for its economic and biological effects to spill over frontiers, has meant that it has been considered in a number of international settings. ACGM and GMAG Members have contributed to these, either by attending the meetings or by advising the officials who have taken part.

THE EUROPEAN COMMUNITY During the 1980s, the European Commission also turned its attention to genetic modification. There were two main reasons:

- the wish of member states to ensure adequate protection across the Community for human health and the environment;
- the need to harmonise standards and set up procedures for the clearance of products for the market, to avoid barriers to trade.

The outcome was the adoption in 1990 of two Council directives on genetic modification, one dealing with activities in containment and the other with release and marketing. Both of them:

- set up procedures for the notification to national authorities of proposals to work with or release genetically modified organisms, and for consent to be required in certain cases;
- require the assessment of risk and the provision of suitable control measures;
- make arrangements for an exchange of information between member states, and for the collective agreement of member states before a product can be marketed.

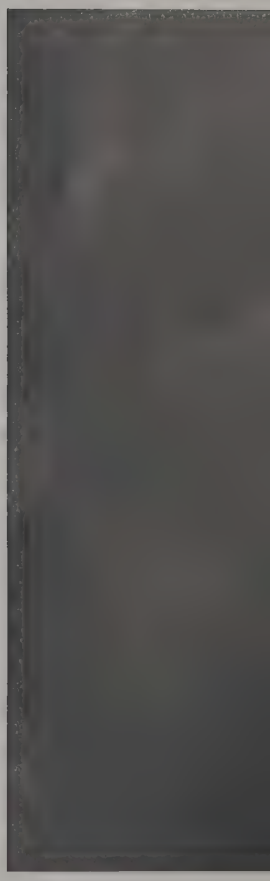
The directives have to be put into effect in each member state by means of national law. The implementing legislation in the UK is described on page 16.

THE OECD The guidelines prepared by the OECD in 1986, on industrial, agricultural and environmental applications of genetic modification, have already been mentioned. They were drawn up by the Group of National Experts on Safety in Biotechnology, established by the OECD's Committee on Science and Technology Policy. The same group went on to study and produce reports and guidance on a number of other subjects such as good developmental principles for experimental releases, the scale up of crop plant releases (to cover large trials of potential new crop varieties), the safety evaluation of novel foods, aspects of vaccine safety and other areas of deliberate release.

Recently the Group of National Experts has been reformed as a new Working Party on Biotechnology, with a remit extending beyond the safety aspects upon which it previously concentrated. Among other subjects it will consider the use of genetically modified organisms in bioremediation, the use of transgenic animals in medicine, and intellectual property rights associated with biotechnology innovation.

UNITED NATIONS The pressures that have brought genetic modification before the OECD and the EC have also thrust it on to the global stage. The United Nations Conference on Environment and Development (UNCED), held at Rio in June 1992, devoted some of its proceedings to biotechnology. Chapter 16 of Agenda 21 recognised that biotechnology could contribute substantially to sustainable development by improvements in food supply, health care and environmental protection.

In parallel, the relevance of genetic modification to global biodiversity has brought it within the scope of the UN Environment Programme's Convention on Biological Diversity. Important political questions arise from the uneven distribution of biological resources and advanced technological expertise among the countries of the world. Efforts are being made to establish principles of international co-operation that will take account of this, to ensure that organisms and knowledge can be shared for the common good.

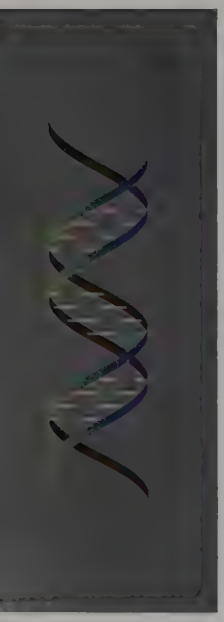


CURRENT STRUCTU

The current UK law on genetic modification is divided into two main areas, covering:

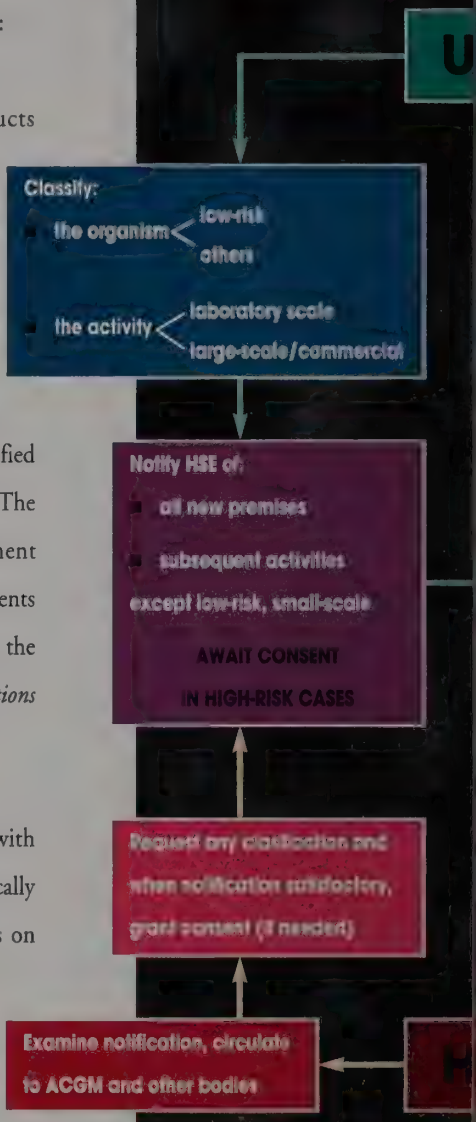
- activities in which organisms are prevented from escaping, or 'contained use';
- the deliberate release of modified organisms or the marketing of products containing them.

It is closely modelled on EC directives which divide in the same way. In contrast to earlier UK legislation it requires the protection not only of human health but also the environment, and forbids certain contained uses and all releases unless consent has been obtained.

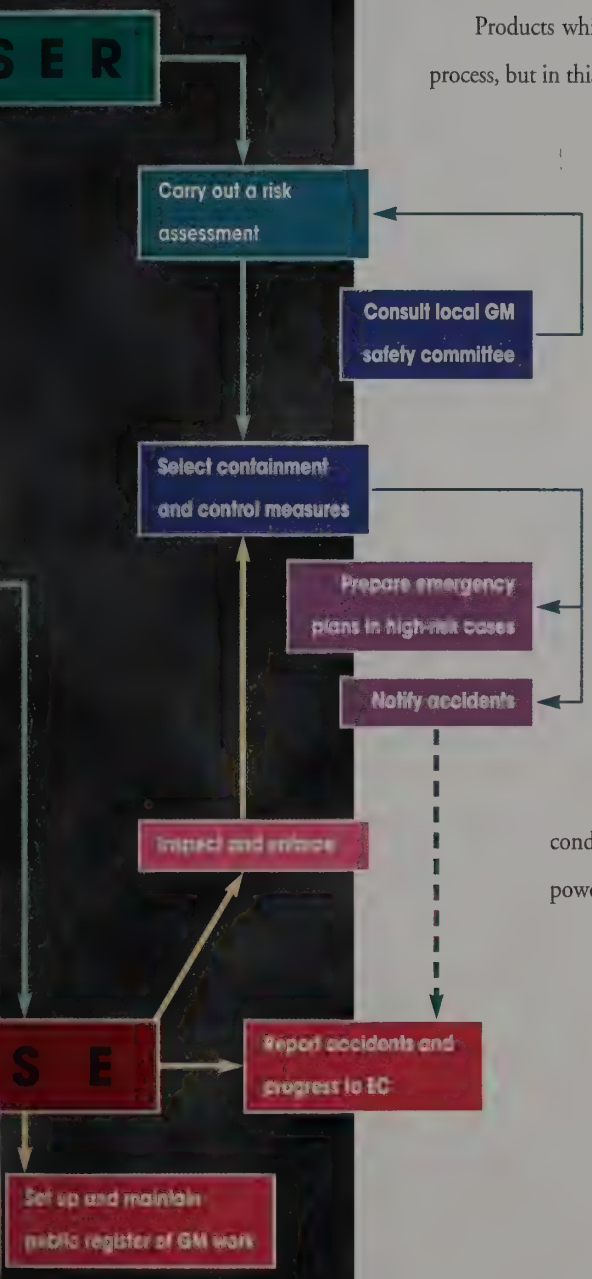


CONTAINED USE Contained use is dealt with by the Genetically Modified Organisms (Contained Use) Regulations 1992 which are made under the HSW Act. The emphasis in them is on risk assessment and the selection of suitable containment measures, with notification requirements to allow this to be checked. The main elements of the Regulations and the duties they impose on the user and on HSE are shown in the diagram; fuller details can be found in the latest *Guide to the Contained Use Regulations* (see Further information section).

RELEASE AND MARKETING Release and marketing are dealt with mainly by the Environmental Protection Act 1990 in combination with the Genetically Modified Organisms (Deliberate Release) Regulations 1992. The emphasis here is on risk assessment and consent, because of the impossibility of recalling most organisms once they have been released. Before a genetically modified organism may be released, a dossier of information about the organism and its effects must be submitted to the Secretary of State, and his consent given. Notice of the application is also given to other bodies concerned with environmental protection. There are provisions for making information available to the public and for the exchange of information within the EC.

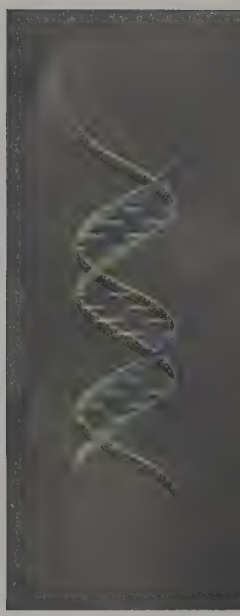


RE OF CONTROLS



Products which are to be placed on the market must pass through a similar consent process, but in this case the agreement of other EC member states must also be obtained, as the product will be freely traded within the Community. The marketing of some products containing genetically modified organisms is covered by separate legislation specific to those products and dealing with risks other than those associated with genetic modification (medicines for example), and this approach is likely to be used more in the future.

ENFORCEMENT The enforcement of the law dealing specifically with genetic modification is carried out by the Health and Safety Executive. For the legislation on release this is done on behalf of the DoE under a special arrangement. HSE has a team of specialist inspectors who are allocated specifically to this work. They inspect premises where contained use activities are carried out and where releases take place, checking the adequacy of safeguards and that consent conditions are being complied with. They have available to them a range of powers and enforcement sanctions for use if advice and persuasion fail.



Genetic modification raises a number of issues of great public interest and importance as well as those of health and safety and environmental protection. Many of these are subject to regulatory control under other statutes and there are other advisory committees on which members of ACGM serve. In any event, ACGM is an important contributor to the bodies involved in those issues, and a channel for the exchange of advice and information.

GENE THERAPY One exciting opportunity for genetic modification is the area of gene therapy where research has the potential to bring major advances to the diagnosis and eventually the treatment of a wide range of serious diseases.

In 1992, the Committee on the Ethics of Gene Therapy, under the chairmanship of Sir Cecil Clothier, examined not only its potential but further concerns which it presents. The key recommendation of the committee was to lead to the establishment of the Gene Therapy Advisory Committee (GTAC) in 1993. Chaired by Professor Dame June Lloyd, with a Secretariat in the Department of Health, GTAC's role is to advise on the ethical acceptability of any proposal to conduct gene therapy research on human subjects

By the end of 1994, GTAC had reviewed 12 proposals for gene therapy research and had approved a total of ten protocols dealing with cystic fibrosis, severe inherited immunodeficiency and three forms of cancer.

GTAC has cross membership with ACGM and close contact is maintained between the two Secretariats. The committee published its first guidance notes in 1994 describing the role of GTAC and the procedures to be followed in seeking approval to conduct gene therapy research on human subjects. A first annual report of the committee's activities has also been published (see Further information section).

NOVEL FOODS The Advisory Committee on Novel Foods and Processes (ACNFP) was formed in 1988 to advise Ministers on novel foods (including, but not exclusively, those produced by genetic modification) and novel food processes. The

ACNFP advises on the safety of genetic modification foods notified under voluntary arrangements in the UK. It has some members in common with ACGM and the two committees work closely in certain areas. Past examples have included genetic modification of yeast intended for bread-making and brewing.

ACNFP publishes an annual report and reports on subjects such as the use of antibiotic resistance markers in foods.

In 1992, ministers set up a committee to consider the ethical concerns surrounding genetically modified foods. The committee was chaired by the Reverend John Polkinghorne and reported in 1993 (see Further information section). It concluded that, while there were no overriding ethical objections to the genetic modification of food organisms, provision should be made for the labelling of foods containing 'ethically sensitive copy genes' to enable the consumer to make an informed choice.

Gene therapy research: scientists analyse human DNA sequences prepared by the technique of gel electrophoresis

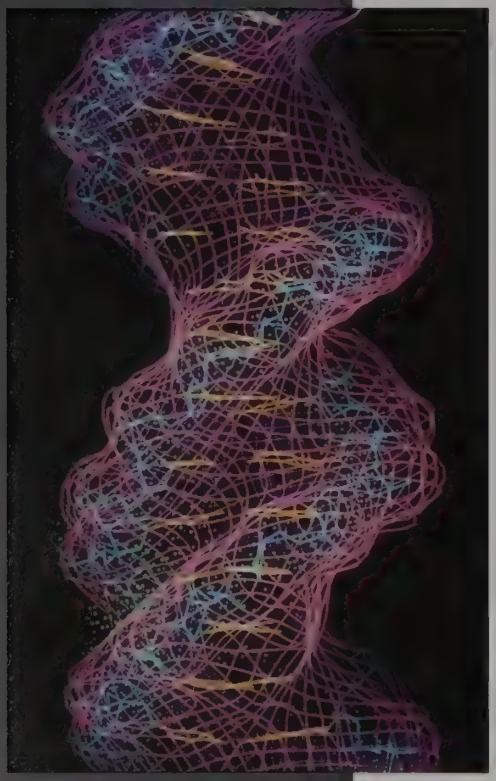
GENETIC SCREENING Genetic screening is sometimes confused with genetic modification but is quite different. It means attempting to predict whether people are likely to suffer from inherited diseases, or be susceptible to particular harmful agents, by examining their genetic make-up. It raises difficult ethical and other questions, involving employment protection, confidentiality, and the effects of this sort of knowledge on a person's insurability and (not least) peace of mind. A fuller discussion of the issues raised by genetic screening can be found in the report of the Nuffield Council on Bioethics (see Further information section).

TRANSGENIC ANIMALS Some aspects of the genetic modification of animals concern risks to human beings and the environment and fall within the scope of the rest of this booklet. There are also issues of animal welfare and the ethics of manipulating living creatures in this way, however. These are examined in the report of the Committee to Consider the Ethical Implications of Emerging Technologies in the Breeding of Farm Animals, under the Chairmanship of Professor Michael Banner.

WHERE NEXT?

Making detailed predictions in a revolutionary field like genetic modification is rash, but some things can be said with a fair amount of confidence.

The science and technology will continue to develop rapidly, and in unforeseen directions. (We might compare the modern proliferation of microchips and computers with the early days of electronic computers. Who could have foreseen where that would lead?) Knowledge of the processes that take place at molecular level within the living cell, and our ability to manipulate and harness them, will increase many-fold. Some of this research, such as the study of human or animal disease, may involve some new risks, but the deeper uncertainties and corresponding anxieties of the past are unlikely to recur.



Computer graphic representation of a short section of DNA

As genetic modification becomes established it will increasingly spread from the research sphere into the release and marketing of organisms and products, and into mainstream industrial processes and other broad fields of application, for example in medicine. It is likely to become commonplace, underlying other activities in the way that, say, computers and microchips are now components of many everyday appliances.

Legislative controls will become increasingly refined where they are applied specifically to genetic modification, but it is likely also that some activities, techniques and classes of organism will be dealt with by more general health, safety and environmental legislation as they are no longer seen to need special treatment. There will need to be some further globalisation of regulatory and other controls, in recognition of the needs of international trade and the difficulty of containing living organisms behind frontiers.

It is important as this process takes place that sound and scientifically based safety principles are worked out and incorporated into law where necessary. ACGM will play a key role in developing those principles.

APPENDIX: MEMBERSHIP OF ACGM

CHAIRMEN

Professor Sir Hans Kornberg	(1986 - 1995)
Sir Robert Williams	(1984 - 1986)

MEMBERS

Professor P Boseley	CBI	(1993 - 1994)	Professor A Atkinson	Specialist	(1984 - date)
Professor G Bulfield	RC	(1990 - date)	Professor J Beringer	Specialist	(1986 - date)
Professor D Burke	CVCP	(1987 - date)	Professor M R W Brown	Specialist	(1984 - 1987)
Mr J A Gilby	CBI	(1984 - 1987)*	Dr N H Carey	Specialist	(1984 - date)
Professor J M Hearn	RC	(1987 - 1989)	Professor P H Clarke	Specialist	(1984 - 1986)
Professor Sir David Hopwood	RC	(1984 - 1987)	Dr E C Dart	Specialist	(1986 - date)
Dr J Ingle	RC	(1984)*	Mr C R Franks	Specialist	(1987 - date)
Professor J R Quayle	CVCP	(1985 - 1987)	Dr E M Hamilton	Specialist	(1984 - 1987)
Dr B M Richards	CBI	(1984 - date)	Professor D J Jeffries	Specialist	(1988 - date)
Professor M H Richmond	CVCP	(1984 - 1985)*	Dr C A C Pickering	Specialist	(1984 - 1987)
Dr G M Schofield	CBI	(1990 - 1993)	Dr J D Pitts	Specialist	(1990 - date)
Dr R Skinner	CBI	(1994 - date)	Professor T M Roberts	Specialist	(1993 - date)
Mr John Thorley	CBI	(1987 - date)	Dr I Taylor	Specialist	(1989 - 1993)
Mrs D Carey	TUC	(1993 - date)	Professor D W Tempest	Specialist	(1987 - 1990)
Dr G Evans	TUC	(1985 - 1992)	Dr E Thorpe	Specialist	(1984)
Lady Haber Kornberg	TUC	(1984 - 1995)*	Sir David Weatherall	Specialist	(1987 - 1988)
Dr J Kinderlerer	TUC	(1984 - date)	Dr N Wilkie	Specialist	(1984 - 1990)
Dr R Owen	TUC	(1984 - date)*	Professor A R Williamson	Specialist	(1984 - 1989)
Mr A W Whybrow	TUC	(1985 - date)	Mr S Vranch	Specialist	(1993 - date)
Professor R Williamson	TUC	(1984 - 1985)*			

Since its inception in 1984, ACGM has followed the normal tripartite structure used for all HSC advisory committees. In addition to an independent Chairman, [illegible] members are nominated by employer[illegible] (the Confederation of British Industry (CB[illegible]) research councils (RC) and the Commit[illegible] of University Vice-Chancellors and Principals (CVCP)); five are nominated by employees (the Trades Union Congress (TUC)) and the remainder are chosen for expertise in a broad range of scientific disciplines. The list shows all Chairmen and members since 1984, their affiliations and an indication of whether they also served on GMAG (shown by *).

The committee also includes assessors from other government departments who have an interest in genetic modification. The current list of assessors includes the Department of the Environment, Department of Health, Department of Trade and Industry, Ministry of Agriculture, Fisheries and Foods, the Scottish Office, the Welsh Office and the Department of Economic Development, Northern Ireland.

The Secretariat of the committee is provided by HSE's Biotechnology Policy section of the Health Policy Division.

GENERAL SCIENCE TEXTS

British Medical Association *Our genetic future: The science and ethics of genetic technology* Oxford University Press 1992 ISBN 0192861565

Davis B D *The genetic revolution: Scientific prospects and public perceptions* Johns Hopkins University Press 1991 ISBN 0801842395

Ministry of Agriculture, Fisheries and Food *Genetic modification and food* FoodSense leaflet PB2052, HMSO 1995

REGULATORY AND SAFETY ISSUES

Department of the Environment/Advisory Committee on Releases to the Environment *The regulation and control of the deliberate release of genetically modified organisms (GMOs)* Guidance Note 1 Department of the Environment 1993

Department of the Environment *Government response to the seventh report of the House of Lords Select Committee on Science and Technology. Regulation of the United Kingdom biotechnology industry and global competetiveness* HMSO 1994 ISBN 0 10 125282 X

Genetic Manipulation Advisory Group *First report of the Genetic Manipulation Advisory Group* (Cmnd. 7215), HMSO 1978 ISBN 0 10 172150 1

Genetic Manipulation Advisory Group *Second report of the Genetic Manipulation Advisory Group* (Cmnd. 7785), HMSO 1979 ISBN 0 10 177850 3

Genetic Manipulation Advisory Group *Third report of the Genetic Manipulation Advisory Group* (Cmnd. 8665), HMSO 1982 ISBN 0 10 186650 X

House of Lords Select Committee on Science and Technology *Regulation of the United Kingdom biotechnology industry and global competitiveness (seventh report)* HMSO 1993 ISBN 0 10 408093 0

HSE *A guide to the Genetically Modified Organisms (Contained Use) Regulations* 1992 L29 HSE Books 1993 ISBN 0 11 882049 4

Recombinant DNA safety considerations OECD, Paris 1986 ISBN 9264128573

Safety considerations for biotechnology 1992 OECD, Paris 1992 ISBN 926413641X

OTHER RELEVANT REPORTS AND GUIDELINES

Advisory Committee on Novel Foods and Processes/Department of Health and Ministry of Agriculture, Fisheries and Food *Report on the use of antibiotic resistance markers in genetically modified food organisms* 1994

Advisory Committee on Novel Foods and Processes/Department of Health *Guidelines on the assessment of novel foods and processes* HMSO 1991 ISBN 0 11 321336 0

Committee on the Ethics of Gene Therapy *Report of the Committee on the Ethics of Gene Therapy* (Cmnd 1788), HMSO 1992 ISBN 0 10 117882 4

Department of Health *Annual report of the Gene Therapy Advisory Committee: November 1993 to December 1994* 1995

Department of the Environment *Advisory Committee on Releases to the Environment, Annual Report No 1: 1993-1994* 1994

Ministry of Agriculture, Fisheries and Food *Report of the Committee on the Ethics of Genetic Modification and Food Use* HMSO 1993 ISBN 0 11 242954 8

Ministry of Agriculture, Fisheries and Food *Report of the Committee to Consider the Ethical Implications of Emerging Technologies in the Breeding of Farm Animals* HMSO 1995 ISBN 0 11 242965 3

Nuffield Council on Bioethics *Genetic screening: ethical issues* 1993 ISBN 0952270102

Royal Commission on Environmental Pollution *Thirteenth report: The release of genetically engineered organisms to the environment* HMSO 1989 ISBN 0 10 1072023

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The compendium of ACGM guidance notes is available free from the ACGM Secretariat, Health Policy Division, Rose Court, 2 Southwark Bridge, London SE1 9HS Tel: 0171 717 6337

GLOSSARY

ACRE Advisory Committee on Releases to the Environment - a statutory committee which advises the Secretary of State on all applications to deliberately release or market a GMO.

ANTIBIOTIC Chemicals which kill or inhibit micro-organisms. Some micro-organisms contain genes which produce resistance to some antibiotics and these often form part of the vector to allow GMOs that contain the modified genes to be readily identified.

BIOCHEMISTRY The study of the chemical reactions in living organisms.

BIODIVERSITY The different species and varieties of organisms generally found in complex ecosystems. In this context, it relates to the desire to maintain a pool of genetic diversity in developing economies and the environment.

BIOREMEDIATION Using organisms (natural or modified) to degrade toxic pollutants.

BIOTECHNOLOGY The use of living organisms, or molecules derived from them, to produce goods, it covers traditional technologies such as brewing and bread-making as well as high technology applications such as vaccine and drug production.

CLONING The use of genetic modification techniques to produce identical copies of a DNA sequence.

DNA An abbreviation for deoxyribonucleic acid, the complex chemical consisting of four repeating subunits which encodes the genetic information in most organisms.

ENZYMES Proteins which catalyse chemical reactions in cells.

GENE A discrete inherited part of the DNA molecule which generally encodes for a single protein or has a controlling function.

GENE THERAPY The introduction of a new gene or the repair of a defective gene in a person's cells in order to provide a missing function or to combat disease or disability

GENETIC MODIFICATION A general description for a variety of artificial and natural techniques which can be used to alter the properties of an organism's genes and hence its characteristics. Sometimes popularly called 'genetic engineering'.

GENETICS The science of inherited characteristics in organisms.

MOLECULAR BIOLOGY The study of living cells at the level of molecules, including the studies on the structure and function of DNA, genes and proteins.

OECD Organisation for Economic Co-operation and Development which consists of most Western European countries, the USA, Canada, Australia, New Zealand and Japan.

PHAGES Viruses which infect bacteria. Their simple biology and small size meant that they were extensively studied during the early years of molecular biology and genetic modification.

PLASMIDS Sequences of DNA which exist independently in bacteria and which have been used as vectors in genetic modification.

PRSC Planned Release Sub-Committee (of ACGM) which was formed in 1986 to consider guidance on the deliberate release of GMOs into the environment and to evaluate notifications. In 1990 it was replaced by ACRE.

SEQUENCING When applied to DNA, this is the analysis of the order of the four chemicals which form DNA and which encode all of the information in genes.

TRANSGENIC ANIMALS Experimental animals which have been genetically modified before birth.

VECTORS A biological system used to transfer genes into an organism so that it will either be incorporated into its own DNA or will independently reproduce and be inherited when the cell divides.

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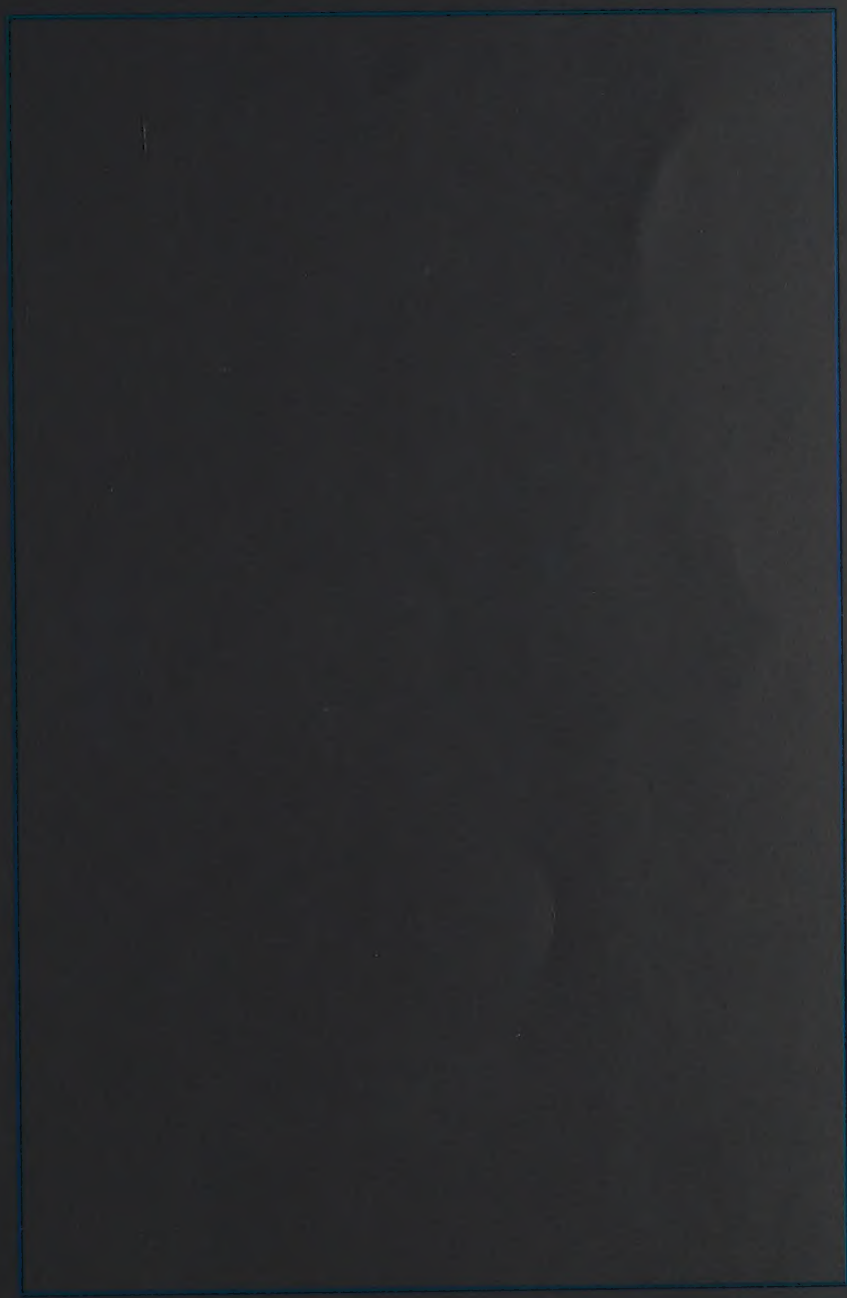

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